IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of
Mamoru OHASHI et al
Serial No : 09/529,715
Filed : April 19, 2000
For : FAST-DISSOLVING PHARMACEUTICAL COMPOSITION

Group Art Unit:1616
Examiner : Sharmila Gollamudi

DECLARATION (E)

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

I, Mamoru OHASHI, a citizen of Japan residing at 10-23-501, Ogaki 6-chome, Ritto-shi, Shiga-ken, Japan, declare as follows.

1. I was graduated from Kyoto Pharmaceutical University in March 1988, and completed the master's course at the same university in March 1990.

Since April 1990 up till the present, I have been an employee of Dainippon Pharmaceutical Co., Ltd. and had been engaged in researches and developments of drug product formulation, particularly in solid dosage form in Pharmaceutical Research Laboratory of said company.

2. I am one of the co-inventors for the invention described in U.S Serial No. 09/529,715 and am familiar with the subject matter thereof.

3. I have read the cited Negoro el al., U.S. patent 5,258,382, Muller et al. U.S. Patent 5,858,410, Arbuthnot et al., U.S Patent 6,458,811 and Shneider et al., U.S. Patent 5,356,636 and am familiar with the subject matter thereof.

4. Under my supervision, the following comparative experiments have been done for the purpose of showing that AS-3201 alone is stable but when it contacts to common pharmaceutical excipients, it becomes unstable and

that a pharmaceutical formulation of AS-3201 containing an acid is more stable than a pharmaceutical formulation containing no acid.

AS-3201 means (R)-2-(4-bromo-2-fluorobenzyl)-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrazine-4-spiro-3'-pyrrolidine-1,2',3,5'-tetrone.

Experiment 1: Interactions between AS-3201 and pharmaceutical excipients

(1) Preparation of test samples

AS-3201 crystals prepared in a similar manner as disclosed in Example 1 of Negoro et al., U.S. Patent 5,258,382 were micronized using Single Truck Jet Mill (manufactured by SEISHIN ENTERPRISE Co., Ltd.) with compression air pressure of 6 kgf/cm^2 to give powders (Lot No. R93004). The microparticles of AS-3201 (mean particle size 1.5μm) was mixed with excipients listed in Table 1 by an agate mortar and the resulting powder was compressed into a disc (100 mg/disc) using a single tableting machine (Type 2B, Kikusui Seisakusho Ltd., Japan, punch size ϕ 6.5 mm).

(2) Stability test

The compressed mixtures were stored for a month at 50°C/75%RH open conditions (without stopper). The color change and degradation amount of the stored samples were measured.

Color change	:	The color differences (ΔE) of the compressed mixtures were measured by a colorimeter (Type SZ-Σ90, C/2 Lump, Nippon Denshoku, Japan).
Assay of related substances	:	Related substances (i.e. degradation products of AS-3201) were assayed by an HPLC method. To the samples exposed to storage conditions, acetonitrile was added to dissolve the drug substance. After added internal standard (I.S.), corresponding 2μg of AS-3201 was injected in HPLC. The amount of related substances was calculated by the following equation.

$$\text{Degradation (\%)} = \frac{\text{Area(Total)} - \text{Area(AS-3201)} - \text{Area(I.S.)}}{\text{Area(Total)} - \text{Area(I.S.)}} \times 100$$

wherein Area (Total) means total peak area during 2—30 min of retention time, Area (AS-3201) means peak area of AS-3201 (ca.10 min of retention time), and Area (I.S.) means peak area of I.S. (ca.20 min of retention time).

The HPLC conditions were as follows:

Column: Develosil ODS (5μm in particle diameter, ϕ 5 mm i.d. x 150 mm in length)
Column temp.: A constant temperature of about 40°C
Mobile Phase: Acetonitrile/0.1 M acetic acid–ammonia buffer (pH3.5, 1/1)
Flow rate: 1.0 mL/min
Wavelength: 296 nm

(3) Test results.

The test results are shown in Table 1.

Table 1 Stability of AS-3201 alone and of mixture with excipients

Component		Ratio [2]	Color Change (ΔE)	Degradation (%) [3]
Product name, Grade	Compendial name			
AS-3201 alone	——	1 : 0	0.4	0.2
Primojel	Sodium carboxymethyl starch	1 : 9	1.9	7.8
Ac-Di-Sol	Croscarmellose sodium	1 : 9	6.4	5.0
Polyplasdone XL	Crospovidone	1 : 9	2.1	47.0
HPC	Hydroxypropylcellulose	1 : 1	4.6	5.0
TC-5RW	Hydroxypropylmethylcellulose 2910	1 : 1	1.0	1.8
PVP K-30	Povidone	1 : 1	3.0	11.1
SFAE (S-370)	Sucrose esters of fatty acids	1 : 1	6.0	2.7
Aerosil 200[1]	Light anhydrous silicic acid	1 : 1	6.3	3.6

1) AS-3201 was only mixed with Aerosil by agate mortar due to its incompressibility

2) The drug-to-excipient ratios of the mixture were 1 or 9, which is generally formulated in tablets.
3) AS-3201 raw powder contained 0.2% of related substances before stored at humidified conditions.

As shown in Table 1, AS-3201 drug substance alone was chemically stable under humidified conditions. The majority of excipients caused increase of the degradation products of the drug substance. In particular, with respect to Polyplasdone and PVP, the degradation percentage of the mixtures were increased up to 47.0% and 11.1%, respectively.

Experiment 2: Stabilization with an acid

(1) Preparation of pharmaceutical formulations

Using the AS-3201 particles (means particle size, 1.5 μm) prepared in Experiment 1(1), pharmaceutical compositions containing an acid (Formulation A to E) and pharmaceutical compositions containing no acid (Formulation 1 to 5) were prepared with the formulae as shown in Table 2 by the following methods (i) to (v).

(i) Preparation of Formulation A and 1 (Tablets)

Formulation A :

AS-3201, lactose and cornstarch were charged in a high-shear granulator, and the mixture was granulated with a solution of tartaric acid in a 10% aqueous polyvinyl alcohol solution. The granules were dried, and thereto was added magnesium stearate, and the resultant was blended in a V-blender. The mixture was compressed on a rotary tableting machine (Cleanpress, Correct 19K, Kikusui Seisakusyo Ltd., Japan) to give tablets (weighing 100 mg, content of AS-3201: 1 mg/tablet).

Formulation 1 :

Tablets were prepared in the same manner as in the above Formulation A excepting replacing tartaric acid by the same amount of lactose.

(ii) Preparation of Formulation B and 2 (Tablets)

Formulation B :

AS-3201, fumaric acid, D-mannitol, carboxymethyl starch sodium

and hydroxypropylcellulose were mixed in a V-blender, and thereto was added magnesium stearate, and the resultant was mixed. The mixture was compressed on a single-punch tableting machine (Type 2B, Kikusui Seisakusho Ltd., Japan) to give tablets (weighing 100 mg, content of AS-3201: 1 mg/tablet).

Formulation 2 :

Tablets were prepared in the same manner as in the above Formulation B excepting replacing fumaric acid by the same amount of D-mannitol.

(iii) Preparation of Formulation C and 3 (Capsules)

Formulation C :

AS-3201, carmellose calcium and lactic acid were mixed well in a mortar, and the mixture was screened through a 30 mesh sieve. To the mixture were added lactose and hydroxypropylmethylcellulose 2910, and the resulting mixture was blended in a V-blender. To the resultant was added magnesium stearate, and the mixture was further mixed. The mixture was filled into a No. 3 capsule in an amount of 180 mg per capsule to give capsules (content of AS-3201: 1.8 mg/capsule).

Formulation 3 :

Capsules were prepared in the same manner as in the above Formulation C excepting replacing lactic acid by the same amount of lactose.

(iv) Preparation of Formulation D and 4 (Powders)

Formulation D :

AS-3201, lactose and low substituted hydroxypropylcellulose were charged into a fluid bed granulator and drier, and the mixture was granulated by spraying thereto a solution of citric acid in a 5% aqueous hydroxypropylcellulose 2910 solution. After drying, the resultant was screened through a 30 mesh sieve to give 1% AS-3201-containing powders.

Formulation 4 :

Powders were prepared in the same manner as in the above Formulation D excepting replacing citric acid by the same amount of lactose.

(v) Preparation of Formulation E and 5 (Tablets)

Formulation E :

AS-3201, lactose and low substituted hydroxypropylcellulose were charged in a fluid bed granulator and drier, and the mixture was granulated by spraying thereto a solution of phosphoric acid in a 5% aqueous hydroxypropylcellulose solution. The granules were dried, and thereto was added magnesium stearate, and the resultant was blended in a V-blender. The mixture was compressed on a rotary tableting machine (Cleanpress, Correct 19K, Kikusui Seisakusyo Ltd., Japan) to give tablets (weighing 100 mg, content AS-3201: 1 mg/tablet).

Formulation 5 :

Tablets were prepared in the same manner as in the above Formulation E excepting replacing phosphoric acid by the same amount of lactose.

(2) Stability Test

The pharmaceutical compositions obtained by Experiment 2(1) were put into a glass bottle without stopper and stored at 50°C/75%RH for one month. The amount of degradation products of AS-3201 was measured and the degradation percentage was calculated in the same manner as in Experiment 1. The results are shown in Table 2.

Table 2 Comparison of degradation percentage of AS-3201 in the presence or absence of an acid

Components	Formulation									
	A	1	B	2	C	3	D	4	E	5
AS-3201 (g)	10		1		1		10		10	
Lactose (g)	740	750	—		75	76	740	770	740	750
D-Mannitol (g)	—		70	75	—		—		—	
Cornstarch (g)	200		—		—		—		—	
Carboxymethyl starch Na (g)	—		20		—		—		—	
Carmellose Ca (g)	—		—		20		—		—	
L-HPC (g)	—		—		—		200		200	
PVA (g)	20		—		—		—		—	
HPC (g)	—		2		—		20		20	
HPMC (g)	—		—		2		—		—	
Magnesium stearate (g)	20		2		1		—		20	
Tartaric acid (g) (pKa=2.93)	10	—	—		—		—		—	
Fumaric acid (g) (pKa=3.03)	—		5	—	—		—		—	
Lactic acid (g) (pKa=3.86)	—		—		1	—	—		—	
Citric acid (g) (pKa=3.13)	—		—		—		30	—	—	
Phosphoric acid (g) (pKa=2.15)	—		—		—		—		10	—
Degradation (%) (50°C/75%RH for 1 month)	0.8	14.1	9.0	27.0	1.0	4.7	1.3	19.8	0.5	19.8

L-HPC : Low substituted hydroxypropylcellulose
PVA : Polyvinyl alcohol
HPC : Hydroxypropylcellulose
HPMC : Hydroxypropylmethylcellulose 2910

In the above Table 2, the pharmaceutical formulations of Formulation A, B, C, D and E contained an acid, and the pharmaceutical formulations of Formulation 1 to 5 did not contain an acid. As is clear from the test results shown in Table 2, when the preparations contained an acid having a pKa value of below 5.6, the degradation of AS-3201 was significantly inhibited.

I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United Stated Code, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 19 day of May, 2005

Mamoru Ohashi

Mamoru Ohashi

Appendix 2-1

#19C YC 4-25-02

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Renee Y. Edwards
Type or print name of person signing certification

Renee Y. Edwards April 9, 2002
Signature Date

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Arbuthnot, *et al.*	
Serial No.	: 08/812,896	Group Art Unit: 1625
Filed	: March 10, 1997	
For	: BENZOTHIOPHENES, FORMULATIONS CONTAINING SAME, AND METHODS	Examiner: Chang, C.
Docket No.	: X-10443	

Response under 37 C.F.R. §1.111

Assistant Commissioner for Patents
Arlington, VA 22202

Sir:

This letter is written in response to the Office Action dated October 10, 2001. Attached hereto is a petition for a three-month extension of time under 37 C.F.R. §1.136. The petition authorizes the Patent Office to charge deposit account No. 05-0840, in the name of Eli Lilly and Company, the necessary fee under 37 C.F.R. §1.17(a)(3) for said three-month extension.

Amendments

Cancel claims 3, 12-18 and 24.

The following amendments to claims 1, 4 and 23 are presented in clean form pursuant to 37 C.F.R. §1.121 (c)(1).

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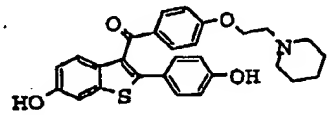
01 FC:117 920.00 CH

1. (Amended) A compound of formula I



(I)

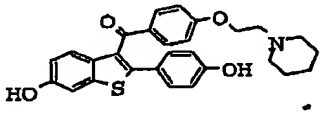
T,0800 C1

and pharmaceutically acceptable salts and solvates thereof, characterized in that the compound is in particulate form, said particles having a mean particle size of less than about 25 microns, at least about 90% of said particles have a size of less than about 50 microns.

C2 3 4. (Amended) The compound of Claim 2 wherein at least 90% of said particles have a size of less than about 35 microns.

1 23. (Amended) A non-solvated crystalline hydrochloride salt of a compound of formula I

T,0801 C3



(I)

characterized in that the compound is in particulate form, said particles having a mean particle size of between about 5 and about 20 microns, at least about 90% of said particles having a size of less than about 35 microns.

Please add new claims 32-38.

11 ~~32~~. A compound of Claim 1 which is non-solvated crystalline 6-hydroxy-2-(4-hydroxy-phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride.

12 ~~33~~. A method of inhibiting osteoporosis comprising administering an effective amount of a compound of claim 1 to a person in need thereof.

13 ~~34~~. A method of lowering serum lipid levels comprising administering a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, to a person in need thereof.

C4

14 ~~35~~. A method for preventing breast cancer comprising administering to a woman in need thereof an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof.

15 ~~36~~. A method of inhibiting osteoporosis comprising administering an effective amount of a compound of claim 7 ~~33~~ to a person in need thereof.

16 ~~37~~. A method of lowering serum lipid levels comprising administering a compound of claim ~~33~~ 7 or a pharmaceutically acceptable salt or solvate thereof, to a person in need thereof.

17 ~~38~~. A method for preventing breast cancer comprising administering to a woman in need thereof an effective amount of a compound of claim ~~33~~ 7 or a pharmaceutically acceptable salt or solvate thereof.

C

Introduction

Claims 1-7, 12-18 and 23-27 are pending.

Claims 3, 12-18 and 24 have been cancelled herewith.

Claims 1, 4 and 23 have been amended herewith. The amendment to claim 1 incorporates the limitations of claim 3 and the amendment to claim 4 adjusts its dependency accordingly. The amendment to claim 1 is supported within the specification at least at page 4, lines 15-29. The amendment to claim 23 is supported within the specification at least at page 22, lines 11-14. Therefore, Applicants submit that no new matter is added via these amendments.

Claims 32-38 have been proposed for entry. New claim 32 is supported within the specification at least at page 22, lines 11-14. New claims 33-35 and 36-38 substantively correspond to original claims 8-10 and 28-30, respectively. Therefore, Applicants submit that no new matter will be added upon entry of these new claims.

Claims 1-7, 12-18 and 23-27 stand rejected under 35 U.S.C. §103(a) over U.S. Patent No.'s 4,133,814, 4,418,068, 5,731,327 and 5,811,120 (Jones I, Jones II, Luke and Gibson, respectively) in view of Lieberman supplemented with U.S. Patent No. 5,202,129 (Samejima). Of these claims only claims 1, 2, 4-7, 23 and 25-27 are still pending.

Claims 1, 2, 4-7, 23 and 25-27 stand rejected under the judicially created doctrine of obvious-type double patenting (JCDOTDP) over the claims in Jones I, Jones II, Luke and Gibson in view of Lieberman and Samejima.

Remarks

The Rejection Under 35 U.S.C. §103(a)

Claims 1, 2, 4-7, 23 and 25-27 stand rejected under 35 U.S.C. §103(a) over Jones I, Jones II, Luke and Gibson in view of Lieberman supplemented with Samejima. Applicants respectfully traverse this rejection and request withdrawal of same.

Claims 1, 2, 4-7, 23 and 25-27 relate to 6-hydroxy-2-(4-hydroxyphenyl)-3-([2-piperidin-1-ylethoxy]benzoyl)benzo[b]thiophene (raloxifene), and pharmaceutically acceptable salts and solvates thereof, particularly non-solvated crystalline raloxifene hydrochloride, within specific particle size parameters.

Jones I, Jones II, Luke and Gibson all describe raloxifene hydrochloride but none of these references describe raloxifene, or a salt or solvate thereof, within the particle size parameters claimed herein.

Samejima relates generally to a "process for micronizing slightly soluble drug".

Lieberman relates generally to the process of "size reduction", *i.e.*, "reducing larger size solid unit masses to smaller size unit masses by mechanical means".

The Examiner considered claims 1, 2, 4-7, 23 and 25-27 obvious in view of these references because,

> Jones I, Jones II and Luke disclosed the claimed compound and Gibson disclosed the pharmaceutical formulations comprising raloxifene hydrochloride and inert carrier. The difference between the instant claims and Jones I, Jones II, Luke and Gibson is that a specific particle size was incorporated.

> Size reduction is a desirable conventional formulation process for pharmaceuticals (see Lieberman p. 110-112), especially for drugs with low water solubility. ... Specifically, Lieberman taught that fluid energy mill/micronization is a method of size reduction of pharmaceuticals; size reduction is desirable since increase of particle resolution enhances bioavailability of poorly soluble drug (p.453). However, one should not always assume that finer particles will always exhibit faster dissolution rate but seeks optimum in sizing for maximum dissolution.
>
> Therefore, one having ordinary skill in the art ... would be motivated to employ the conventional size reduction process in micronization to prepare the pharmaceutical formulation for raloxifene. Especially such formulation has been prepared (see Gibson formulation 5-115) using a granulation aide which will result in micronized particle size (see Samejima whole article especially col. 3 lines 27-30)
>
> In absence of unexpected results it is prima facie obvious to employ a micronized particle size formulation of a known drug which has poor solubility for its known activity because such micronized particles are expected to improve the rate of dissolution and enhance bioavailability.

For the reasons set forth below, Applicants respectfully assert that the Examiner has not articulated a case of *prima facie* obviousness against the present claims.

Citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, (Fed. Cir. 1986) for authority, the Manuel of Patent Examining Procedure (MPEP) at §2141 mandates that when applying 35 U.S.C. §103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;
(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and
(D) Reasonable expectation of success is the standard with which obviousness is determined.

With respect to tenet "(D)", Applicants respectfully assert that the Examiner has misconstrued the definition of "success" in the present circumstances and, consequently, has not taken into account certain aspects of the references cited, *i.e.*, those aspects casting doubt on the artisan's expectations prior to the filing date of the present case.

Applicants do not contest the Examiner's assertion that the skilled artisan would be motivated to reduce the particle size of a poorly soluble drug, and would be in possession of the required particle size reducing technology, in order to do so. Indeed, on page 39, lines 25-36 of the present application the following passage is found:

> Often, compounds with poor solubility profiles can have their bioavailability enhanced by increasing the surface area of the formulated particles. The surface area generally increases per unit volume as the particle size decreases. Various techniques for grinding or milling a drug substance are well known in the art and each of these techniques are commonly used to decrease particle size and increase the surface area of the particle. It would seem reasonable that the best way to deal with any slightly soluble compound would be to mill it to the smallest size possible; **however, this is not always practical or desirable.** (Emphasis Added).

As laid out in more detail below, however, Applicants respectfully assert that "success" in the present

circumstances is not achieving an increased dissolution rate by reducing particle size but is more appropriately characterized as whether or not it would be practical, on a commercial manufacturing scale, to do so.

Continuing at line 36, page 39, the specification states,

> The milling process has an economic cost not only it [*sic*] the direct cost of the process, itself, but also with other associated factors. For example, very finely divided material presents difficulties and cost in capsule filling or tablet preparation, because the material will not flow, but becomes caked in finishing machinery. Such finishing difficulties generate non-homogeneity in the final product, which is not acceptable for a drug substance. Additionally, the milling process, physically generates heat and pressure on the material, such conditions lead to chemical degradation of the compound, thus such milling techniques are usually kept to a minimum.
>
> Therefore, there is always dynamic [tension] between the properties which yield the maximum bioavailability (particle surface area) and the practical limits of manufacture. **The point of compromise which marks this "best solution" is unique to each situation and unique as to its determination.** (Emphasis added).

In addition, Lieberman at page 110 states,

> Size reduction and scale-up problems in the pharmaceutical industry are very similar to those found in "heavy industry," and are more often solved empirically rather than through the theoretical route.

Furthermore, Samejima, in column 2, lines 32-35 and lines 43-47, states,

> [The difficulty in obtaining particles finer than several micromolar] is associated with [the] peculiar nature inherent to micronized particles that such particles have a tendency to aggregate, adhere, or solidify as the particle size decreases.
>
> The present inventors have found that ultrafine particles of a slightly-soluble drug ... can be easily obtained by grinding [micronizing] the drug in the presence of a grinding aid selected from ....

With respect to micronization as a particle size reducing technology technique in general (**a technique not employed by Applicants to produce the material claimed**) the disputed Omelczuk reference (*Eur. J. Pharm. and Biopharm.*, 43:95-100, 1997) which was published more than five years after the invention of Samejima was placed in the state of the art (see EP 411629), states,

> Although micronization offers this advantage (maximization of particle size area), it can precipitate formulation processing problems because of high dust, low density, and poor flow properties as compared with conventionally milled powders.

Applicants respectfully assert that the formulation problems associated with maximizing particle size area were obviously not eradicated by the invention of Samejima.

To sum up, Applicants respectfully assert that although the art cited teaches that reducing the particle size of a slightly soluble compound should increase its dissolution rate and potentially its bioavailability, it also teaches that reducing the size of a drug could cause problems in effective formulation of the material. Applicants respectfully submit

that a reasonable expectation of success, based on the references cited, to find a particle size range which: 1) would be easily, economically, and consistently achievable on commercial scale; 2) would be amenable to easy, economical, and consistent commercial formulation into tablets; and 3) would offer an acceptable dissolution/bioavailability profile was not present as of the filing date of the present application. The absence of this requisite expectation of success mitigates against a finding that the presently claimed material is *prima facie* obvious in view of Jones I, Jones II, Luke, Gibson, Lieberman, Samejima, alone or in combination.

Even assuming *arguendo* that the present claims are *prima facie* obvious in spite of the above discussion, Applicants respectfully assert that certain properties of the claimed material offer it unexpected advantages in the bulk production/development of non-solvated crystalline raloxifene hydrochloride. A thorough discussion of these advantages is laid out within the specification at pages 43-54 and is summarized below.

Two related physical properties of a bulk drug that can alter the dissolution rate of a dosage form are particle size and surface area. The impact of the surface area, which is a function of particle size, is illustrated by the Noyes-Whitney equation (see page 44, lines 4-9). Simply put, the Noyes-Whitney equation predicts that the greater the surface area, the faster the rate of dissolution. Therefore, this principle would suggest decreases in particle size should lead to increases in dissolution rate.

Applicants assessed the dissolution of tablets containing crystalline non-solvated raloxifene hydrochloride as a function of particle size and found that within the parameters claimed, there is an insignificant effect on the dissolution profiles thus obtained (see discussion at pages 51-53). Applicants hypothesize that this unexpected behavior

arises from the fact that, although over this range the particle size changes, the effective surface area does not. This property of the claimed material is particularly beneficial in that one can formulate non-solvated crystalline raloxifene hydrochloride within the parameters claimed and expect said material to have substantially similar dissolution profiles.

This similarity in dissolution profiles is a particularly advantageous property of the claimed material when one considers that for non-solvated crystalline raloxifene hydrochloride there was a high *in vitro* to *in vivo* correlation between dissolution and average area under the curve (AUC) values obtained in two different animal species (see pages 45-50). In other words, dissolution profiles for non-solvated crystalline raloxifene hydrochloride were demonstrated to be excellent surrogate markers for bioavailability in these pre-clinical models. These pre-clinical models are in turn surrogate markers for clinical bioavailability. Thus, a separate clinical study designed to determine the pharmacodynamic effects of particle size in humans is theoretically not necessary as long as one formulates the non-solvated crystalline raloxifene hydrochloride within the parameters described in the claims.

In fact, non-solvated crystalline raloxifene hydrochloride is the active ingredient in Evista® which is currently marketed in the United States and dozens of other countries for the prevention and treatment of osteoporosis. This marketed drug is formulated using material described in the present claims. To date, not one regulatory agency has required a clinical study designed to determine the effect of particle size on pharmacodynamics so long as the active ingredient within the material sought to be registered is that described in the present claims, especially claims 23 and 25. These marketing approvals (all obtained after the present

application was filed and all obtained without the additional clinical study described above) confirm the valuable nature of the present invention.

Applicants respectfully assert that the discussion above is sufficient to rebut a finding that the present claims are *prima facie* obvious in view of Jones I, Jones II, Luke, Gibson, Lieberman, and Samejima, alone or in combination. Applicants respectfully request reconsideration and ultimate withdrawal of the present rejection.

The Rejection Under the JCDOTDP

Claims 1, 2, 4-7, 23 and 25-27 stand rejected under the JCDOTDP over the claims in Jones I, Jones II, Luke and Gibson in view of Lieberman and Samejima. Applicant's comments above with respect to the obviousness of the present claims under 35 U.S.C. §103(a) are incorporated fully herewith. Applicants respectfully assert that in view of this incorporated discussion, the present claims are not obvious variations of those issued from Jones I, Jones II, Luke or Gibson. Applicants respectfully request withdrawal of this rejection.

Some Final Comments Regarding New Claims 33-38

Applicant notes that the subject matter of proposed claims 33-38 was restricted from the present claims during initial prosecution of this case. Applicants assert that in view of their comments above in support of the patentability of claims 1 and 23, and in further view of the precedent set in In re Ochai, 71 F.3d 1565, 37 USPQ2d 1127, (Fed.Cir.1995), it is proper to re-join the subject matter of new claims 33-38 with claims 1 and 23 since said new claims are directed to using compounds co-extensive in scope with the novel and unobvious compounds of claims 1 and 23.

Conclusion

Applicants respectfully assert that claims 1, 2, 4-7, 23, 25-27 and 32-38 are in condition for allowance and respectfully request reconsideration and allowance of same.

Respectfully submitted,

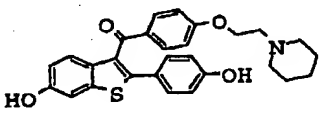
Gilbert T. Voy
Attorney for Applicants
Registration No. 43,972
Phone: 317-276-2966

Eli Lilly and Company
Patent Division/GTV
Lilly Corporate Center
Indianapolis, Indiana 46285

April 9, 2002

Appendix A: Amended Claims With Markings Indicating Changes Made Pursuant to 37 C.F.R. §1.121(c)(1)(ii)

1. (Amended) A compound of formula I

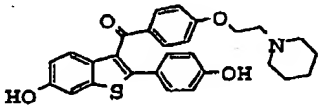


(I)

and pharmaceutically acceptable salts and solvates thereof, characterized in that the compound is in particulate form, said particles having a mean particle size of less than about 25 microns**, at least about 90% of said particles have a size of less than about 50 microns**.

4. (Amended) The compound of Claim ~~3~~ 2 wherein at least 90% of said particles have a size of less than about 35 microns.

23. (Amended) A **non-solvated crystalline hydrochloride salt of a** compound of formula I

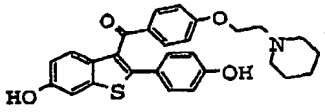


(I)

~~and pharmaceutically acceptable salts and solvates thereof,~~ characterized in that the compound is in particulate form, said particles having a mean particle size of between about 5 and about 20 microns, at least about 90% of said particles having a size of less than about 35 microns.

Appendix B: Clean Copy of Pending Claims

1. A compound of formula I



(I)

and pharmaceutically acceptable salts and solvates thereof, characterized in that the compound is in particulate form, said particles having a mean particle size of less than about 25 microns, at least about 90% of said particles have a size of less than about 50 microns.

2. The compound of Claim 1 wherein said particles have a mean particle size of between 5 and about 20 microns.

4. The compound of Claim 2 wherein at least 90% of said particles have a size of less than about 35 microns.

5. The compound of Claim 1 which is the non-solvated crystalline 6-hydroxy-2-(4-hydroxy-phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride having substantially the following X-ray diffraction pattern obtained with copper radiation:

d-line spacing (Angstroms)	I/I_o (x100)
13.3864	71.31
9.3598	33.16
8.4625	2.08
7.3888	7.57
6.9907	5.80
6.6346	51.04

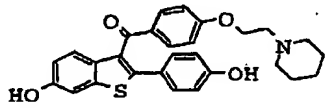
6.1717	29.57
5.9975	5.67
5.9135	9.87
5.6467	38.47
5.4773	10.54
5.2994	4.74
4.8680	4.03
4.7910	5.98
4.6614	57.50
4.5052	5.75
4.3701	9.03
4.2516	69.99
4.2059	57.64
4.1740	65.07
4.0819	12.44
3.9673	22.53
3.9318	100.00
3.8775	9.07
3.7096	33.38
3.6561	21.65
3.5576	3.36
3.5037	7.97
3.4522	18.02
3.4138	4.65
3.2738	10.23
3.1857	8.90
3.1333	6.24
3.0831	9.43
3.0025	12.13
2.9437	4.96
2.8642	7.70
2.7904	11.95
2.7246	3.05
2.6652	3.32

2.5882 7.30.

6. A pharmaceutical formulation comprising or formulated using the compound of Claim 5 and one or more pharmaceutically-acceptable carriers, diluents, or excipients.

7. A pharmaceutical composition comprising or formulated using a compound according to Claim 1, or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients.

23. A non-solvated crystalline hydrochloride salt of a compound of formula I



(I)

characterized in that the compound is in particulate form, said particles having a mean particle size of between about 5 and about 20 microns, at least about 90% of said particles having a size of less than about 35 microns.

25. A compound of Claim 23 which is the non-solvated crystalline 6-hydroxy-2-(4-hydroxy-phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b] thiophene hydrochloride, having substantially the following x-ray diffraction pattern obtained with copper radiation:

d-line spacing (Angstroms)	I/I_o (x100)
13.3864	71.31
9.3598	33.16

8.4625	2.08
7.3888	7.57
6.9907	5.80
6.6346	51.04
6.1717	29.57
5.9975	5.67
5.9135	9.87
5.6467	38.47
5.4773	10.54
5.2994	4.74
4.8680	4.03
4.7910	5.98
4.6614	57.50
4.5052	5.75
4.3701	9.03
4.2516	69.99
4.2059	57.64
4.1740	65.07
4.0819	12.44
3.9673	22.53
3.9318	100.00
3.8775	9.07
3.7096	33.38
3.6561	21.65
3.5576	3.36
3.5037	7.97
3.4522	18.02
3.4138	4.65
3.2738	10.23
3.1857	8.90
3.1333	6.24
3.0831	9.43
3.0025	12.13
2.9437	4.96

2.8642	7.70
2.7904	11.95
2.7246	3.05
2.6652	3.32
2.5882	7.30.

26. A pharmaceutical formulation comprising or formulated using the compound of Claim 25 and one or more pharmaceutically-acceptable carriers, diluents, or excipients.

27. A pharmaceutical composition comprising or formulated using a compound according to Claim 23, with one or more pharmaceutically acceptable carriers, diluents or excipients.

32. A compound of Claim 1 which is non-solvated crystalline 6-hydroxy-2-(4-hydroxy-phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride.

33. A method of inhibiting osteoporosis comprising administering an effective amount of a compound of claim 1 to a person in need thereof.

34. A method of lowering serum lipid levels comprising administering a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, to a person in need thereof.

35. A method for preventing breast cancer comprising administering to a woman in need thereof an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof.

36. A method of inhibiting osteoporosis comprising administering an effective amount of a compound of claim 23 to a person in need thereof.

37. A method of lowering serum lipid levels comprising administering a compound of claim 23, or a pharmaceutically acceptable salt or solvate thereof, to a person in need thereof.

38. A method for preventing breast cancer comprising administering to a woman in need thereof an effective amount of a compound of claim 23, or a pharmaceutically acceptable salt or solvate thereof.

Appendix 2-2

Notice of Allowability	Application No. 08/812,860	Applicant(s) Arbuthnot et al.
	Examiner Celia Chang	Art Unit 1625

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *04/09/02 amendment*.
2. ☒ The allowed claim(s) is/are *1, 2, 4-7, 23, 25-27, and 32-38*.
3. ☐ The drawings filed on _____ are accepted by the Examiner.
4. ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____.
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   *Certified copies not received: _____.
5. ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
8. ☐ CORRECTED DRAWINGS must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. _____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment/Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the top margin (not the back) of each sheet. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.
9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1 ☐ Notice of References Cited (PTO-892)
2 ☐ Notice of Informal Patent Application (PTO-152)
3 ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
4 ☐ Interview Summary (PTO-413), Paper No. _____.
5 ☐ Information Disclosure Statement(s) (PTO-1449), Paper No(s). _____
6 ☐ Examiner's Amendment/Comment
7 ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8 ☒ Examiner's Statement of Reasons for Allowance
9 ☐ Other

DETAILED ACTION

1. Amendment and response filed by applicants in Paper No. 17 dated April 25, 2002 have been entered and considered carefully. Claims 3, 12-18 and 24 have been canceled. Claims 1-2, 4-7, 23, 25-27 are pending. Claims 32-28 have been presented for rejoining when the base claims 1-2, 4-7, 23, 25-27 become allowable.

2. ***Reason for Allowance***

The following is an examiner's statement of reasons for allowance:

Applicants have amended claims 1-2, 4-7, 23 and 25-27 to a particular range of particle size. Although prior art of record taught that size reduction in general is prima facie obvious approach to increase dissolution rate but the selection of a particular range of particle size are more often solved empirically rather than through theoretical route. The particular range further evidenced unexpected results in view of the unexpected behavior of the claimed compounds because within the parameters claimed, there is an insignificant effect on the dissolution profiles, thus, a separate clinical study designed to determine the pharmacodynamic effects of particle size in humans is not necessary (see specification p.45-50). Thus, the incorporation of the particular size of the claims has obviated the 103(a) rejection or the obviousness type double patenting rejections. Claims 1-2, 4-7, 23, 25-27 and 32-38 are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 703-308-4702. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

WPPC/Chang
May 29, 2002

Celia Chang
Primary Examiner
Art Unit 1625